REMARKS

Support for amendments

Support for the amendments can be found in original claims 1-4. No new matter has been added. Claims 5, 9, 30 and 31 have been withdrawn; claims 1, 3, 4, 42-53 and 54 are pending.

Substance of the interview

Applicants' representatives wish to thank Examiner Yaen for telephone conversation on July 16, 2003. At that time, a provisional election was made with traverse to prosecute the Group I, SEQ ID NO:4, Claims 1-4. Applicants confirm the election.

REQUEST FOR RECONSIDERATION

Angiogenesis--the growth of new vessels from pre-existing vessels--is a complex phenomenon that occurs in distinct phases and relies upon modulation or expression of variety of intracellular proteins, extracellular matrix components, proteases, inflammatory molecules, chemokinases, molecules involved in cell division and proliferation, cytoskeletal rearrangement, adhesion and apoptosis. Identification of nucleic acid sequences and the encoded polypeptides that are associated with angiogenesis is important because of their usefulness in promoting wound healing, facilitating organ transplantation, and treating myocardial infarction, tumors, diabetic retinopathy, macular degeneration, psoriasis, and rheumatoid arthritis.

Angiogenesis plays an important role not only in the usual biological process of homeostasis, but also in a variety of diseases and disorders, including tumor growth and metastasis. Since angiogenesis can link tumor cells to a host's circulatory system, thus promoting tumor growth, controlling tumor vascularization can provide a way to prevent or reduce tumor size. The claimed invention provides polypeptides, such as hBAZF (SEQ ID NO:4), that can be used as therapeutic targets to modulate angiogenesis (for example, the polypeptide of SEQ IDNO:4 can be used to generate antibodies which can be administered to halt or diminish tumor growth by inhibiting vascularization), to prevent or diminish tumor growth, as well as for diagnostics and prognostics (for example, to assess if a wound is healing by testing for angiogenesis before the appearance of blood vessels).

Endothelial cells mediate angiogenesis in a multi-step process during neovascularization. *In vitro* models of angiogenesis are useful for identifying alterations in gene expression involving angiogenesis, as was done here for the claimed invention.

Rejection of claims under 35 U.S.C. § 101 and § 112, first paragraph

Rejection of claims under 35 U.S.C. § 101 is respectfully traversed. The asserted diagnostic and therapeutic utilities for hBAZF meet all of the requirements of the Utility Guidelines: the utility is specific, substantial, and credible.

The utility of the invention is specific: hBAZF is associated with a small class of proteins that were found to be associated with angiogenesis, some surprisingly so. The experiments which yielded SEQ ID NO:4 were designed to specifically reveal those genes differentially regulated during angiogenesis (Kahn *et al.*, *Am. J. Pathol.* 156:1887-900; Yang *et*

al., Am. J. Pathol. 155:887-95). The Example found on page 126, lines 16-31 of the specification indicates that SEQ ID NO:4 is up-regulated during angiogenesis. Because of its high expression during vessel morphogenesis, SEQ ID NO:4 represents an excellent molecular marker of angiogenesis, as well as a therapeutic target to inhibit angiogenesis.

The utility is credible: SEQ ID NO:4 is a credible marker for angiogenesis as well as a therapeutic target, based on examination of an art-accepted model of angiogenesis. SEQ ID NO:4 was discovered in experiments that used an art-accepted model of angiogenesis--the suspension of endothelial cells in type I collagen gels. In this classic system described at least as early as 1983 by Montesano, Orci and Vassali (*J. Cell Biol.* 97:1648-1652), endothelial cells progress through differentiation in a coordinated and synchronized manner. Using a similar model system, Okabe *et al.* noted that analogous to the role of *murine* BAZF in regulating cell proliferation, *human* BAZF (SEQ ID NO:4) plays a role in cell proliferation of HVUE cells when suspended in collagen gels (Okabe *et al., Mol. Cell. Biol.* 18:4235-44). The model system recapitulates *in vivo* angiogenic events *in vitro*, validating the role of SEQ ID NO:4 has in angiogenesis. The claimed utilities for hBAZF are not based simply on homology alone. The function of SEQ ID NO:4, is based on homology, as well as the context in which the polypeptide was discovered--in a model of angiogenesis (see p. 52, line 31 to page 53, line 18, for example).

The utility is substantial: function-blocking antibodies or other function-inhibiting agents against SEQ ID NO:4 can be used to diminish, halt and prevent tumor growth, an important aspect of cancer treatment. Furthermore, assessing and encouraging wound healing that requires angiogenesis is especially important to sufferers of type II diabetes.

The invention meets the criteria of the Utility Guidelines, and one of skill in the art would know how to make and use the invention. Applicants respectfully request withdrawal of this rejection.

The claimed polypeptide of SEQ ID NO:4 exists. First, the sequence of the polypeptide is provided in Table 4, pages 11-12 of the specification. Second, the overwhelming majority of gene transcripts are translated (Alberts, B. 2002. *Molecular biology of the cell.* Garland Science, New York); a logical result, especially in an evolutionary context: cells are unlikely to waste resources on needless gene transcription. The Office has not given an appropriate example of a transcript encoding a polypeptide that is *not* translated; instead, only examples purporting to show post-translational regulation of polypeptides that *do* exist at least some of the time are presented. Alberts *et al.* remark that regulation at the translational level is an exception to the

rule that increases in gene expression correlate with increases in translation (Alberts *et al.* 2002 at p. 435; see also p. 379, 2nd paragraph). No proof that the increased transcription of the polynucleotide which encodes SEQ ID NO:4 does not result in increased translation has been offered. The given examples of the exception to the rule that transcription is the norm for protein expression regulation are based on very unique proteins (iron-binding ferritin), catastrophic exogenous events that are *not* gene specific (radiation's effects on p-glycoprotein expression), and abnormal cancer cells (p53, retinoblasma [*sic*; retinoblastoma] protein). Finally, translation of any gene depends on appropriate RNA secondary structure and the presence of housekeeping gene products, such as initiation factors (ornithine decarboxylase).

To maintain its rejection under 35 U.S.C. § 112, first paragraph, "it is incumbent upon the Patent Office [. . .]to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning. . . " (*In re Marzocchi*, 439 F.2d 220 at 224). The Office has not met its burden to maintain the rejection. The rejection is respectfully requested to be withdrawn.

Rejection of claims under 35 U.S.C. § 112, first paragraph

Rejection of claims under 35 U.S.C. § 112, first paragraph, on the grounds that the written description is inadequate, is respectfully traversed. Adequate guidance is provided whereby one of ordinary skill in the art would select isolated polypeptide sequences with at least 84% amino acid sequence identity with SEQ ID NO:4 which would retain hBAZF activity.

For example, Bowie *et al.* (Bowie, J.U., J.F. Reidhaar-Olson, W.A. Lim, and R.T. Sauer. 1990. Deciphering the message in protein sequences: tolerance to amino acid substitutions. *Science.* 247:1306-10), often cited by the Office, note that while the problem of predicting protein structure from primary sequence, as well as function, can be complex ((Bowie *et al.*, 1990); page 1306, column 1), they also note that certain general principles have been established. These principles can be applied to SEQ ID NO:4 polypeptide variants, which are consistent with the teachings of the specification. These principles fall in the following categories:

(1) The nature of surface *vs.* buried residues in the folded protein;

(2) The hydrophobic nature of core sequences;

(3) The interchangeable nature of surface sites; and

(4) The roles of variant residues in related sequences.

Residues that are buried in the protein require non-polar side chains (Bowie *et al.*, 1990); while surface residue side chains are more interchangeable since few features of side chains are conserved (Bowie *et al.*, 1990). This principle is elegantly illustrated by analysis of the λ repressor: residues that are highly conserved are buried (5 of 6), while those sites that can tolerate many different substitutions are found on the surface (Bowie *et al.*, 1990).

Because of their importance in folding and stability--which are driven by the hydrophobic effect--core sequences require almost exclusively hydrophobic and neutral residues (Bowie *et al.*, 1990). While core sequences are limited to these classes of amino acids, they are mostly interchangeable with each other because the hydrophobic effect does not depend on residue pairing (Bowie *et al.*, 1990). Even within the core, the factors of hydrophobicity, packing volume and steric compatibility are not equally "informative" (Bowie *et al.*, 1990). While physically, these factors are all important, the factor of hydrophobicity of a sequence, rather than the factor of total side chain volume, predicts more about the side chain's acceptability as a member of the core, while the factor of steric compatibility falls midway between the two (Bowie *et al.*, 1990).

Each surface site can accommodate many side-chain substitutions, although most proteins can tolerate only a limited number of hydrophobic substitutions overall (p. 1308, column 1, first full paragraph). This principle is due to the assumption that large patches of hydrophobic surface residues would lead to aggregation (Bowie *et al.*, 1990), which would presumably inhibit function.

A description as filed is presumed to be adequate; unless or until sufficient evidence or reasoning to the contrary has been presented (MPEP § 2163.04, p.2100-173 (February 2003); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). Compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must allow one of ordinary skill in the art to recognize that the applicant has invented what is claimed (MPEP § 2163.02, p. 2100-171 (February 2003); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)). A written description of an invention involving a chemical genus requires a precise definition of the claimed subject matter sufficient to distinguish it from other materials (*Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997)). Since one of skill in the art can distinguish such a formula from others and can identify many of the species that the claims

encompass, such a formula is normally an adequate description of the claimed invention. *Id.* at 1406.

Applicants have provided such a formula. The amino acid sequence of SEQ ID NO:4 is provided on pages 11-12, Table 4. Furthermore, the method for calculating sequence identity, as known to one of skill in the art at the time of filing, has also been provided on page 64, lines 7 to page 65, line 3. The specification teaches how to determine variants of SEQ ID NO:4 by determining sequence identity (page 76, line 22 to page 77, line 5) and the use of conservative amino acids substitutions to make variants (page 67, line 7 to page 69, line 7). The specification provides adequate guidance as to the meaning of "percent amino acid sequence identity" and describes methods for this calculation using available computer software (page 74, line 26 to page 75, line 20 of the specification). One would evaluate a candidate polypeptide as being a variant of SEQ ID NO:4 by determining its sequence identity with SEQ ID NO:4.

Furthermore, because SEQ ID NO:4 has been shown to have specific structural features, even further guidance is provided. SEQ ID NO:4 (hBAZF) has zinc finger motifs, characteristic of the BAZF family (Fukuda *et al.*, *Oncogene* 11:1657-1663: Kerckaet *et al.*, *Nat. Genet.* 5:66-70: Miki *et al.*, *Blood* 83:26-32), a structure known to be highly conserved in many proteins. One would know how to select a variant polypeptide of hBAZF with 84% sequence identity to SEQ ID NO:4 while retaining important structures, such as zinc finger motifs. hBAZF (SEQ ID NO:4) is the human orthlog of mouse BAZF (mBAZF), and therefore, conserved regions should remain invariant.

Krüppel-like factors (KLFs) are zinc finger proteins that are important components of the eukaryotic transcriptional machinery. By regulating the expression of a large number of genes that have GC-rich promoters, KLF transcription factors can take part in cellular function, including cell proliferation, apoptosis, differentiation, and neoplastic transformation. The most characteristic feature of KLF proteins is a highly conserved DNA binding domain (more than 65% sequence identity among family members: Kaczynski *et al.*, *Genome Biology* 4:206-215) at the carboxyl terminus that has three tandem CysCysHisHis zinc finger motifs. Each zinc finger motif conforms to the CysCysHisHis zinc finger consensus sequence C-X_2-5-C-X_3-(F/Y)-X_5-ψ-X_2-H-X_3-5-H, where X represents any amino acid and ψ is a hydrophobic residue (Wolfe *et al.*, *Annu. Rev. Biophys. Biomol. Struc*, 29:183-212). The overall amino-acid similarity between the zinc finger motifs of Sp1 and other members of the Sp1-like/KLF family is a minimum of 66.7%

and the length of each motif is invariant (Kaczynski *et al.*, *Genome Biology* 4:206-215). These proteins all recognize related GC-type elements.

mBAZF contains five repeats of the Krüppel-like zinc finger motif (Okabe *et al.*, 1998). These zinc finger motifs bind specific DNA sequences (Baron *et al.*, *Cancer* 13:221-224). The homology of Bcl6 gene between humans and mice is 100% identity for zinc finger motifs (Fukuda *et al.*, *Oncogene* 11:1657-1663). In addition to the guidance provided in the specification for obtaining variants of BAZF, further guidance is provided when sequence comparisons are made between mBAZF and SEQ ID NO:4 (hBAZF). Because the murine ortholog of hBAZF is known (Fukuda *et al.*, 1995), variants that have a substitution in hBAZF that is found at the analogous position in mBAZF will retain DNA-binding function because of the characteristic zinc finger motifs.

The specification also teaches that the peptide sequence, "RSQ....PQV" present in the human sequence and most likely representing an alternative spliced form of the gene, provides guidance for carefully evaluating variants that have altered this sequence. One would use only the most conservative substitutions or keep these residues invariant.

The objections to claims 1, 3 and 4 have been obviated by appropriate amendment. The rejection of the claims under 35 U.S.C. § 112, second paragraph, and the rejections of the claims under 35 U.S.C. 102(b) have also been obviated by appropriate amendment.

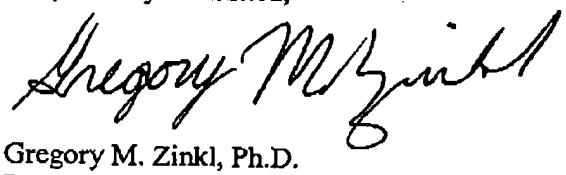
Upon indication of allowable subject matter, Applicants will request rejoinder of non-elected, but dependent, claims.

CONCLUSION

Reconsideration and withdrawal of all claim rejections is respectfully requested. Applicants believe that all claims in the present application are in condition for allowance.

Should the Examiner have any questions, or would like to discuss any matters in connection with the present application, the Examiner is invited to contact the undersigned at (312) 876-8936.

Respectfully submitted,



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